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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,514	01/24/2002	Muriel Moser	DECLE55.1CP2CD	4302

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,514	MOSER ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0-01

DETAILED ACTION

1. Applicant's election of the species dendritic cell (DC) progenitor, filed 2/11/05, with traverse, is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Upon further consideration, all species have been rejoined.

Claims 27-54 are being acted upon.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

A) Uninitialed changes in the residence address of Inventor Lespagnard have been made.

B) It is noted that the declaration has not been dated by Inventor Velu. However, MPEP 602.05 states that a new declaration will no longer be required in instances wherein the date of execution has been omitted.

4. Applicant has claimed the benefit of priority to U.S. Application Nos. 08/414,480, 08/625,507, 09/025,405, 09/049,502, and 09/951,849.

In the instant application the term "dendritic cell" (DC) has been defined twice. At page 4 the term is defined to include "all non-B cells present in purified or enriched preparations of dendritic cells." It is also noted that at page 4 the term is disclosed as being interchangeable with the term "dendritic-like cell." DC is also defined at page 11 as "an isolated dendritic cell or its dendritic progenitor." Note that the second definition, while at first seeming to narrow the scope of the first, does not actually indicate that any of the "non-B cells" of the page 4 definition are intended to be excluded. Indeed, the page 11 definition can be interpreted as broadening the scope of the term to include dendritic progenitors not found in purified or enriched preparations. Accordingly, in the instant context, the term "dendritic cell" is considered to encompass all "non-B cells present in purified

or enriched preparations of dendritic cells" as well as "dendritic progenitors" wherever they may be found.

Given the aforementioned definition of a DC, the instant application cannot be granted the benefit of priority to the '480 parent application as said application does not disclose the broad definition of DC, i.e., "dendritic-like cells", found in the instant application. Additionally, the '480 application does not disclose the activation of generic "immune cells" nor most of the other limitations of the dependent claims, e.g., a method employing DCs of myeloid origin.

Regarding the '507 and '405 applications, the applications do not disclose a method for producing an anti-tumor response in mammalian subjects. Additionally, the applications do not disclose most of the other limitations of the dependent claims, e.g., a method employing DC progenitors nor DCs of lymphoid origin. Accordingly, the priority date of the instant application is the priority date of the '502 application, 3/27/98.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 27-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for producing an anti-tumor response employing a hybrid comprising a mature DC and a tumor cell,

does not reasonably provide enablement for:

a method for producing an anti-tumor response employing a hybrid comprising a DC (including a DC progenitor) and a tumor cell

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by

the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Regarding producing an anti-tumor response, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, e.g., methods of producing an anti-tumor response, a certain amount of enablement beyond mere assertion must be required.

The specification provides insufficient data to enable claims drawn to the method as broadly claimed. Note that the method encompasses the use of *any* type of DC hybrid including hybrids comprising immature DCs and DC progenitors. It is well-established that the stages of DC maturation range from progenitor through precursor, through immature, to mature DCs. Austyn (1996) teaches a minor variation of this concept referring to DC progenitors as being found in the bone marrow or blood, DC precursors and immature DCs as non-lymphoid DCs and migratory DCs, and mature DCs as lymphoid DCs. Most importantly, the reference teaches that freshly isolated non-lymphoid DCs (i.e., any DCs that are less than fully mature) have "little capacity to initiate primary in vitro immune responses" (page 1288). Zhang et al. (1997) extends these functional findings. The reference shows that DC progenitors have no capacity to stimulate T cells (i.e., an immune response), while immature DCs have only a limited capacity to stimulate a T cell response (Figure A). Even Inventor Moser's own work, from as late as 2004, teaches that adoptively

transferred immature DCs, generated *in vitro*, induce a state of non-responsiveness in naïve T cells *in vivo* (de Heusch et al., 2004). Accordingly, the method as broadly claimed, employing *any* type of DC for the induction of an anti-tumor response, must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 27-34 and 45-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman et al. (1994) in view of Guo et al. (1994, IDS) and Sornasse et al. (1992).

Sussman et al. teaches the adoptive transfer of *in vitro* sensitized, activated autologous immune cells (T cells) for treating malignancy, including specific tumors (see particularly, ADOPTIVE IMMUNOTHERAPY, page 297-298). The reference further teaches limitations to be overcome including immunogenicity (or lack thereof) of the specific tumor to be treated, and the need to culture more effector T cells limited by the need for additional tumor stimulator cells (see particularly, **In vitro sensitized cells**, pages 300-302).

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC/tumor cell hybrids for the activation of the immune cells.

Guo et al. teaches a plurality of hybrids (or hybridomas) comprising a bone marrow derived antigen-presenting B cell and a tumor cell(see particularly page 520, columns 2-3). The reference teaches that the hybrids comprise cells that express both tumor-specific antigens and the machinery for antigen presentation (see particularly page 518, column 1), that said hybrids are immunogenic, and that said hybrids induce a protective immune response to tumors that might otherwise "escape immune surveillance because they do not express signals

that are essential for activation of the host immune system" (see particularly page 520, column 1 and page 518, column 1).

Sornasse et al. teaches that , while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses in vivo" [in comparison to B cells] (see page 18, column 1). Note that Sornasse et al. employs DC isolated from spleen which would include DC progenitors, myeloid DCs, and lymphoid DCs.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of adoptive transfer of *in vitro* sensitized, activated autologous immune cells (T cells) for treating malignancy (an anti-tumor response), as taught by Sussman et al, employing DC/tumor cell hybrids for the activation of the immune cells, given the combined teachings of Guo et al. and Sornasse et al. One of ordinary skill in the art at the time of the invention would have been motivated to perform the method of Sussman et al. employing a DC/tumor hybrid for *in vitro* T cell activation because: A) employing an APC/tumor hybrid would address the problem of reduced tumor immunogenicity, i.e., induce a protective immune response to tumors that might otherwise "escape immune surveillance because they do not express signals that are essential for activation of the host immune system", as taught by Guo et al., B) the use of an APC/tumor hybrid would address the problem of insufficient number of effector T cells because the use of an immortalized (and thus, no longer limited) tumor stimulator cell would allow for the unlimited expansion of effector tumor cells, and C) DCs comprise superior antigen presenting capabilities than do B cells, as taught by Sornasse et al. Regarding the limitations of Claims 29-32, routes of administration comprise only the routine optimization of the claimed method and fall well within the purview of the skilled artisan.

9. Claims 35-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman et al. (1994) in view of Guo et al. (1994, IDS) and Sornasse et al. (1992), as applied to Claims 27-34 and 45-54 above, in further view of U.S. Patent No. 5,849,589.

Sussman et al., Guo et al., and Sornasse et al. have been discussed above.

The combined reference teachings differ from the claimed invention only in that they do not teach a method wherein the DCs are induced with GM-CSF to DC characteristics before co-cultivation.

The '589 patent teaches the induction of DC characteristics employing GM-CSF before the use of said DCs for the *ex vivo* expansion of T cells for adoptive immunotherapy (see column 2, lines 19-29 and column 11, lines 15-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the combined method of Sussman et al., Guo et al., and Sornasse et al. employing the GM-CSF-induced DC of the '598 patent. One of ordinary skill in the art would have been motivated to perform said induction of DC characteristics before use because said induction induces the differentiation of DCs into the superior antigen presenting cells of Sornasse et al.

10. Claims 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman et al. (1994) in view of Guo et al. (1994, IDS) and Sornasse et al. (1992), as applied to Claims 27-34 and 45-54 above, in further view of Panja et al. (1993).

Sussman et al., Guo et al., and Sornasse et al. have been discussed above.

The combined reference teachings differ from the claimed invention only in that they do not teach a method wherein the DC/hybrids are irradiated to prevent proliferation before co-cultivation.

Panja et al. teaches the irradiation of stimulator cells before use in co-cultivation (see particularly page 1116, column 1, *Allogeneic Mixed Cell Cultures*).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the combined method of Sussman et al., Guo et al., and Sornasse et al. employing irradiated DC hybrids as stimulators. The use of irradiated stimulator cells was well-known to one of ordinary skill in the art at the time of the invention for the prevention

of stimulator cell proliferation, as demonstrated by Panja et al.

11. Claims 27-40 and 45-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman et al. (1994) in view of Gong et al. (1997).

Sussman has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach a method employing a DC/tumor cell hybrid for the activation of the immune cells.

Gong et al. teaches a GM-CSF induced DC/tumor hybrid capable of activating T cells against unknown tumor associated antigens (see particularly, page 560).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the combined method of Sussman et al., employing the DC tumor hybrid of Gong et al. as the T cell stimulator. One of ordinary skill in the art at the time of the invention would have been motivated to use a DC/tumor hybrid as the stimulator of the T cells because a DC/tumor hybrid is capable of activating T cells against unknown tumor associated antigens, as taught by Gong et al.

12. Claims 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman et al. (1994) in view of Gong et al. (1997), as applied to Claims 27-40 and 45-54 above, in further view of Panja et al. (1993).

Sussman et al. and Gong et al. have been discussed above.

The combined reference teachings differ from the claimed invention only in that they do not teach a method wherein the DC/hybrids are irradiated to prevent proliferation before co-cultivation.

Panja et al. teaches the irradiation of stimulator cells before use in co-cultivation (see particularly page 1116, column 1, *Allogeneic Mixed Cell Cultures*).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform

the combined method of Sussman et al. and Gong et al., employing irradiated DC hybrids as stimulators. The use of irradiated stimulator cells was well-known to one of ordinary skill in the art at the time of the invention for the prevention of stimulator cell proliferation, as demonstrated by Panja et al.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

15. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

6/9/05

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